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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/637,430	08/08/2003	Mario R. W. Ehlers		2673

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MARIO R. EHLERS
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EXAMINER

NASHED, NASHAAT T

ART UNIT PAPER NUMBER

1656

DATE MAILED: 02/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/637,430

Applicant(s)

EHLERS ET AL.

Examiner

Nashaat T. Nashed, Ph. D.

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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Claims 1-20 are pending and under consideration.

The disclosure is objected to because of the following informalities: The accepted acronym for carboxypeptidase A is "CPA" and not "CPDA", see page 8, last paragraph. Appropriate correction is required.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-20 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. The claimed method requires knowledge of the three-dimensional structure of angiotensin-converting enzyme (ACE). The three dimensional structure of ACE is neither disclosed in the application nor known in the prior art. Thus, the claimed method is inoperative and could not be carried out by any one.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-20 are directed to a method for design and synthesis of domain-selective of ACE using the three dimensional structure for ACE. The specification does not describe the three-dimensional structure for ACE, and the prior art does not teach any. Also, the specification fails to teach any crystal of any ACE from any biological source, which diffracts X-ray sufficiently for structure determination. It is noted that the specification teaches the recombinant preparation of a mutant in which undefined 36-amino acid residues have been removed and truncated after residue Ser-625. Thus, the exact amino acid sequence, which is used to crystallize in example 2. It is not clear from example 2 whether a crystal suitable for structure determination by the X-ray diffraction method was obtained or not. Neither the crystal of ACE nor its complex with any inhibitor is described in the specification by any of its characteristics such as the space group or the cell unit dimension. In addition, claims 4, 5, 14 and 15 are directed

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to a method wherein the ACT is prepared by peptide synthesis. The testicular enzyme contains >700 amino acid residues. No one in the prior art was able to chemically synthesize an enzyme larger than ~100 amino acid residues. The specification does not teach any new technology for the preparation of up to 700 amino acid residues enzyme, which is enzymatically active. In addition, the enzyme require at least one glycosyl residue at the glycosylation cites, see Yu *et al.*, last paragraph at page 3519, which the specification is silent on how to achieve the introduction of the glycosyl residues into said enzyme.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals of any ACT from any biological source purified from its natural source or recombinantly expressed in any host cell including crystals of ACT-inhibitor complex. Factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any method to obtain any crystal ACT or its inhibitor complex from any biological source. The specification provides guidance and examples in the form of an assay to crystallize a mutant ACT with undisclosed amino acid sequence (see example 1) and its crystallization unnder the specific crystallization condition in example 2. While molecular biological techniques and genetic manipulation to make any protein are known in the prior art, many ACT inhibitors are known and commercially available and the skill of the artisan are well developed, knowledge regarding the three-dimensional structure of ACT, and crystallization of ACT proteins and their complexes is lacking. ACE has been of considerable interest for over 25 year, as its inhibitors are known drugs for lowering blood pressure. The specification states at page 3:

" Despite intensive efforts by numerous academic and industry research groups over many years, the ACE crystal structure could not be solved. This has largely been due to the inability to generate ACE proteins, from natural or recombinant sources, that can yield crystals suitable for high-resolution x-ray diffraction. It is anticipated that once ACE proteins can be crystallized, the three-dimensional x-ray structure can be determined and solved rapidly."

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It is well established in the art that obtaining a protein and/or its complexes in a crystal form is highly unpredictable. The skilled artisan would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, its mutants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallizable. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success is extremely low. It should be noted the cited teaching of the specification above clearly show that many attempts to crystallize the wild-type enzyme purified from its natural source has failed, and the specification has not describe the crystallization of any wild-type enzyme. The amount of experimentation to identify an ACT protein from any biological source or its mutant, which can be crystallized alone or in complex with its inhibitor, and identify a crystal suitable structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization condition or mutants which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences of the ACT or its specific mutant and the exact crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2-6 and 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejection:

- (a) Claims 2-6, and 12-15 contain the phrase "e.g." which renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).
- (b) Claims 2-6, and 12-15 the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

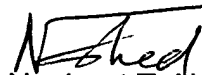
No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Nashaat T. Nashed, Ph. D.
Primary Examiner
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